REMARKS

The Present Invention

The present invention pertains to a water-soluble compound, a composition thereof, a method of treating cancer with the water-soluble compound, and a method of preparing a water-soluble compound.

The Pending Claims

Claims 63, 65, 66, 68-70, 72, 73, 75-77, 79-81, 83-87, 90, 91, and 107-129 are currently pending. Claims 63, 65, 66, 68-70, 72, and 128 are directed towards the water-soluble compound. Claims 73, 75, and 76 are directed towards the composition comprising the water-soluble compound. Claims 77, 79, 80, and 107-118 are directed towards a method of treating cancer with the water-soluble compound. Claims 119-127 are directed towards a method of inhibiting heat shock protein 90 (Hsp90) with the water-soluble compound. Finally, claims 81, 83-87, 90, 91, and 129 are directed towards the method of preparing a water-soluble compound.

Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the present invention. In particular, claims 63 and 81 have been amended to recite that A is geldanamycin or a derivative thereof, as supported by the specification at, for example, page 11, lines 17-24. Claims 72 and 90 have been amended to recite that the drug is geldanamycin. Claims 107-109 and 119-128 have been added and are supported by the specification at, for example, page 2, lines 5-12. Claims 110-118 have been added and are supported by the specification at, for example, page 40, line 32, through page 43, line 13. Abstracts are submitted herewith (i.e., Naef et al., *Int. J. Cancer*, 66(3): 315-321 (1996); Imura et al., *Blood*, 89(8): 2951-2958 (1997)) that disclose that, at the time the application was filed, N87 cells were known to be associated with gastric carcinoma and Hut102 cells were known to be associated with adult T-cell leukemia. Finally, claims 128 and 129 have been added and are supported by the specification at, for example, page 11, lines 17-24. No new matter has been added by way of these amendments.

Summary of the Office Action

Regarding the election/restriction, the Office alleges that there is no known defined genus of a macrolide or ansamacrolide for which the search could be expanded. Claims 63, 65, 66, 68-70, 72, 73, 75-77, 79-81, 83-87, 90, and 91 have been rejected under 35 U.S.C. §

112, second paragraph, as allegedly indefinite. Finally, the Office has rejected claims 77, 79, and 80 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Reconsideration of the pending claims is respectfully requested.

Discussion of the Election/Restriction and Improper Markush Rejection

The Office states that the search was conducted using groups for A that were exemplified in the specification. The Office further advises that the structure on page 13 of the specification should be added to the claims. The claims have been amended to include the geldanamycin derivatives as specified in the application. Therefore, this objection is believed to be moot.

Discussion of the Section 112, second paragraph, Rejection

The Office rejects claims 63, 65, 66, 68-70, 72, 73, 75-77, 79-81, 83-87, 90, and 91 as indefinite because of the definition of substituent X and drug A. With respect to X, the claims already specify that X is a polar moiety selected from the group consisting of an amino acid residue, a peptide residue, a polypeptide residue, and a protein residue. Therefore, the claims provide both functional *and* structural information with regard to X. The amino acid residue, peptide residue, polypeptide residue or protein residue of X contains at least one nucleophilic group (e.g., the thio group on L-cysteine) that is capable of forming a compound as taught by the specification. Moreover, suitable amino acid residues, peptide residues, polypeptide residues, and protein residues are those that help render the compounds of the present invention water-soluble. Accordingly, one of ordinary skill in the art would readily be able to determine what X groups are suitable for use in the present invention in view of the specification and chemistry that is well known in the art. Therefore, in view of the functional and structural language already provided in the claims and the teachings of the specification, Applicants submit that claims 63, 65, 66, 68-70, 72, 73, 75-77, 79-81, 83-87, 90, and 91 are not indefinite with respect to substituent X.

The Office also contends that it is unclear what the metes and bounds of drug A are. The claims have been amended to point out that A is geldanamycin or a derivative thereof, in which the derivative is a compound of the recited formula. The geldanamycin derivatives (i.e., "A") are attached to the rest of the succinimide compound through the amino group at the C-17 position (see, for example, page 16, line 24, through page 17, line 6). The amendment renders the specific rejection of claims 72 and 90 moot as well.

Therefore, in view of the amendments and the foregoing discussion, Applicants submit that the pending claims are clear and definite, and the rejection has been overcome.

Discussion of the Section 112, first paragraph, Rejection

The Office has rejected claims 77, 79, and 80 under Section 112, first paragraph, as allegedly not enabled. Claims 77, 79, and 80 are limited to treating cancers that express Hsp90. Applicants previously demonstrated that, at the time the present application was filed, several cancers were known to express Hsp90 (abstracts resubmitted herewith). The Office now contends that the specific cancers that Applicant discussed are broader than what is specified in the instant application. Moreover, the Office states that geldanamycin is not known to treat the specified cancers (e.g., endometrial carcinoma, breast cancer, leukemia, gastrointestinal cancer, a tumor of the central nervous system, and tongue carcinoma). The rejection of the claims under § 112, first paragraph, is respectfully traversed.

Geldanamycin and derivatives thereof were known to be effective inhibitors of Hsp90 at the time the application was filed. See, for example, Stebbins et al., *Cell*, 239 (1997); Sepehrnia et al., *J. Biol. Chem.*, 271: 15,084 (1996); and Dasgupta et al., *Experimental Cell Research*, 29: 237 (1997). Certain cancers were also known to express Hsp90. See, for example, Franzen et al., *Electrophoresis* 18(3-4): 582-587 (Mar-Apr 1997); Yano et al., *Jpn. J. Cancer Res.* 87(9): 908-915 (1996); Kojika et al., *Leukemia* 10(6): 994-999 (1996); Xiao et al., *J. Tongji Med. Univ.* 16(4): 212-216 (1996); Ehrenfried et al., *Surg. Oncol.* 4(4): 197-203 (1995); Kato et al., *Acta Neuropathol. (Berl)* 89(2): 184-188 (1995); Ito et al. *J. Oral Pathol. Med.* 27(1): 18-22 (Jan. 1998); and Thomas et al. *Br. J. Urol.* 77(3): 367-372 (1996). It has been shown that inhibition of Hsp90 stops uncontrolled cell growth, thereby reducing or slowing cancerous growth. In addition, contrary to the Office's contention, at least geldanamycin and 17-allylamino-17-demethoxygeldanamycin ("17-AAG") have been shown to treat breast cancer, at the time of filing (see, for example, Schulte et al, *Cancer Chemother. Pharmacol.*, 42(4): 273-279 (1998), abstract submitted herewith). In view of the state of the art at the time the present application was filed, and in light of the teachings of the specification of the present application, one skilled in the art would understand and appreciate how to use the claimed compounds to treat cancer that expresses Hsp90 without undue experimentation. Accordingly, the specification is enabled.

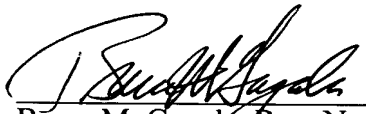
More particularly, Applicants have taught those of ordinary skill in the art how to make and use the present invention. Applicants explain to those of ordinary skill in the art how to make and use the method of claims 77, 79, and 80. Such teaching pertains to water-soluble compounds (see specification at, for example, page 7, line 20, to page 16, line 21), chemical synthesis of the water-soluble compounds (see specification at, for example, page 32, line 7, to page 35, line 3), compositions (see specification at, for example, page 23, line 25, to page 27, line 10), suitable doses (see specification at, for example, page 31, line 17, to page 32, line 5), formulations (see specification at, for example, page 27, line 11, to page 29, line 22), which includes modes of administration, carriers, and concentrations. Moreover, the specification teaches that geldanamycin and its derivatives (compounds to which the pending claims are directed) are known to inhibit Hsp90. Examples 3 and 4 of the instant specification describe the efficacy of water-soluble compounds of the present invention to treat cancers that express Hsp90 (e.g., gastric carcinoma and leukemia). This disclosure reveals to those skilled in the art how to make and use the invention, particularly as defined by pending claims 77, 79, and 80. And those skilled in the art are further taught that the water-soluble drugs, composition, and methods claimed herein are readily applied to other cancers that express Hsp90. Accordingly, Applicants have enabled the claimed invention as required under § 112, first paragraph.

Therefore, in view of the foregoing discussion, pending claims 77, 79, and 80 are enabled by the specification, and the rejection is believed to be moot.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



Bruce M. Gagala, Reg. No. 28,844
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: October 21, 2003